

Impact case study (REF3b)

Institution: The University of Manchester
Unit of Assessment: UoA08 Chemistry
Title of case study: Diffusion-Ordered Spectroscopy
1. Summary of the impact <p>Pioneering research in the UoA has driven significant advances in diffusion-ordered nuclear magnetic resonance spectroscopy (DOSY), resulting in pulse sequence and analysis software that has been commercialised under licence by Agilent, and distributed as open-source software across 68 countries. DOSY has given a manufacturer of NMR equipment a competitive advantage that has contributed to several \$10m's of instrument sales since 2009. These advances have changed <i>practice</i> and <i>capacity</i> in industry, <i>through the introduction of new products and processes</i>: one of the world's largest chemical companies is using the technique in about 30 % of all formulation projects. DOSY is having significant economic impact: one food industry company reporting sales growth of £35m in the REF period as a direct result of the use of DOSY.</p>
2. Underpinning research <p>The key Manchester researchers were:</p> <ul style="list-style-type: none">• Professor Gareth Morris (Reader in Physical Chemistry 1994-1997, Professor of Physical Chemistry 1998 to date);• Dr Mathias Nilsson (postdoctoral research associate 2005-2007, EPSRC Advanced Research Fellow 2007-2012, Lecturer 2012, Reader 2013 to date). <p>The rapid analysis of mixtures of samples by spectroscopic means is a very important chemical function. One method that has been developed at the University of Manchester exploits differences in diffusion rates between mixture components to distinguish their characteristic NMR spectra. The underpinning research has advanced significantly the knowledge and understanding of DOSY NMR techniques and their applications in determining the compositions of multi-component mixtures.</p> <p>The key to mixture analysis using NMR is to be able to distinguish between signals from different species. One distinctive characteristic of a molecule (determined by its size) that can be measured with NMR is its diffusion coefficient, and extending previous work by Charles Johnson we developed methods to produce very high resolution spectra, for example separating the signals of all the different components in a brain extract (e.g. acetate, alanine, lactate, N-acetyl aspartate, glutamate) according to size [1-3].</p> <p>The power of DOSY was greatly increased by our introduction of broadband homonuclear decoupling ("pure shift") methods, which can increase spectral resolution by nearly an order of magnitude [4,5].</p> <p>Our introduction of "matrix-assisted DOSY" [6] extended the method to allow the analysis of mixtures in which species diffuse at the same rate, for example those of isomers, by exploiting differential strengths of interaction with a slowly-diffusing matrix.</p>
3. References to the research <p>The awards of the Royal Society of Chemistry Award in Magnetic Resonance Spectroscopy to Morris and of the BRSG/NMRDG Award for Excellent Contribution to Magnetic Resonance by an Early Career Researcher to Nilsson were based in part on references 1-2 and 4-6 below respectively. Citation numbers taken from Google Scholar (16/9/13).</p>

Key references

1. H. Barjat, G.A. Morris, S. Smart, A.G. Swanson, and S.C.R. Williams, "High Resolution Diffusion Ordered 2D Spectroscopy (HR-DOSY) - A New Tool for the Analysis of Complex Mixtures", *J. Magn. Reson., Ser. B*, 108, 170-172 (1995). [154 citations]. DOI: [dx.doi.org/10.1006/jmrb.1995.1118](https://doi.org/10.1006/jmrb.1995.1118).
2. M.D. Pelta, H. Barjat, G.A. Morris, A.L. Davis and S.J. Hammond, "Pulse Sequences for High Resolution Diffusion-Ordered Spectroscopy (HR-DOSY)", *Magn. Reson. in Chem.*, 36, 706-714 (1998). [167 citations]. DOI: [dx.doi.org/10.1002/\(SICI\)1097-458X\(199810\)36:10<706::AID-OMR363>3.0.CO;2-W](https://doi.org/10.1002/(SICI)1097-458X(199810)36:10<706::AID-OMR363>3.0.CO;2-W).
3. M.D. Pelta, G.A. Morris, M.J. Stchedroff and S.J. Hammond, "A One-Shot Sequence for High Resolution Diffusion Ordered Spectroscopy", *Magn. Reson. in Chem.* 40, S147-S152 (2002). [107 citations]. DOI: [dx.doi.org/10.1002/mrc.1107](https://doi.org/10.1002/mrc.1107).

Other references

4. M. Nilsson and G.A. Morris, "Pure shift Proton DOSY: Diffusion-Ordered 1H Spectra without multiplet structure", *Chem. Commun.* 2007, 933-935. [28 citations]. DOI: [dx.doi.org/10.1039/b617761a](https://doi.org/10.1039/b617761a).
5. S. Faulkner, M. Nilsson and G.A. Morris, "Pure Shift Proton NMR: a Resolution of the Resolution Problem?", *Angew. Chem. Int. Ed.* 49, 3901-3903 (2010). [35 citations]. DOI: [dx.doi.org/10.1002/anie.201001107](https://doi.org/10.1002/anie.201001107).
6. R. Evans, S. Haiber, M. Nilsson and G.A. Morris, "Isomer Resolution by Micelle-Assisted Diffusion-Ordered Spectroscopy", *Anal. Chem.* 81, 4548-4550 (2009). [30 citations]. DOI: [dx.doi.org/10.1021/ac9005777](https://doi.org/10.1021/ac9005777).

4. Details of the impact**Context**

Nuclear magnetic resonance is one of the most important and powerful analytical tools used by chemists. It is able to determine, for example, the composition of a mixture, the structures of complex molecules, and the mobilities of these molecules. However, to direct the complex and precisely-timed sequences of radiofrequency and magnetic field pulses that are used in an NMR spectrometer to measure these different properties of substances is a science in itself. The Impact described in this case relates to the development and commercial exploitation of one such family of pulse sequences, known as DOSY, that is able to analyse complex mixtures in a unique manner that has proved vital to industrial research and product development.

Pathways to impact

The initial impetus for our developments in DOSY came from an industrial collaboration with Pfizer Global Research, and led to dedicated processing software which was initially shared widely but informally with other users. The subsequent development of DOSY software for the proprietary operating system of the major NMR manufacturer Varian (now Agilent) gave both the opportunity to exploit the intellectual property generated, and an effective vehicle for disseminating the results to a wide range of users including many industrial research organisations. Key contributors to this Impact were the School policy of maintaining shared high-resolution NMR facilities, and the assistance of UMIP (University of Manchester Intellectual Property management agent) in negotiating the licensing of DOSY software. In parallel, open-source DOSY processing code was made available through the DOSY Toolbox, which is now in use in 68 countries and has contributed to a significant shift in practice and capacity in industrial research.

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Since the commercialisation of this technique many of the 100 or so papers on DOSY published each year are from industry, but inevitably only a small proportion of industrial use of DOSY is captured by such a metric. *“... the interest in, and use of, DOSY in the pharmaceutical industry is far greater than that evidenced by publications in the public domain. The majority of applications are at later stages of product development, when information on mixture composition is most valuable, and here publishing opportunities are very limited because of confidentiality concerns.”* (Vice-President R&D, Mestrelab Research) [A]

In addition to the widespread use of our data processing software, DOSY experiments developed at Manchester have now been incorporated into the software of almost all commercial high-resolution NMR equipment. *“The overwhelming majority of DOSY users are dealing with mixtures of small organic or inorganic molecules but there are scientists at bio-NMR sites where DOSY is regularly used to monitor molecular associations.”* (Applications Scientist, Agilent) [B]

DOSY NMR has had fundamental impact in a diverse range of important sectors that include pharmaceuticals, fine chemicals, petrochemicals, and flavours and fragrances. *“Mixture analysis using NMR is a large, diverse problem that relies on a number of techniques. DOSY is widely perceived to be vital technology for this purpose.”* (Vice-President R&D, Mestrelab Research) [A]

Impact

The principal impacts associated with DOSY NMR are:

- 1 *“The performance of an existing business has been improved through the introduction of new ... products”.* Our DOSY experimental methods and data processing software have allowed new products to be developed, with major economic impact. For example, the flavourings and fragrances manufacturer Givaudan used DOSY to discover a new flavour ingredient, generating a total sales growth for that product alone of more than 50M CHF (£35m) over the REF period, which is more than 20 % compared to the status quo. (Researcher, Givaudan) [C]
- 2 *“A business or sector has adopted a new or significantly changed technology”.* Our DOSY methods have generated major changes in capacity and practice in industrial research; the last time industry changed its use of NMR to such an extent was with the introduction of multidimensional methods in the 1980s. For example, Givaudan now analyse approximately 20 % of all NMR samples using DOSY. Syngenta, one of the world’s leading agricultural science companies, uses DOSY to assist in reducing the environmental impact associated with the use of its plant-protection products by optimising plant protection formulations, and *“... to measure the rate of diffusion of plant protection compounds in water which will help us understand their breakdown in the environment ... The ‘One-Shot’ sequence [reference 3 above] ... is our preferred method of acquiring DOSY NMR spectra because it increases throughput on our NMR spectrometers.”* (Researcher, Syngenta) [D]. At the multinational chemical manufacturer DuPont, DOSY is now used in *“30% of our projects ... mostly fluorochemical studies, but really studying all kinds of reaction mixtures”* (Researcher, DuPont) [E].
- 3 *“The performance of an existing business has been improved through ... the adoption of new, updated or enhanced technical standards and/or protocols”.* Manchester’s collaborative research and development of DOSY NMR software with Varian (now Agilent) has positioned that company as a leading global supplier of commercial DOSY NMR software. Software developed specifically for Varian spectrometers was first licensed to them in 2001 in a barter deal. In 2010, Varian licensed through the University of Manchester’s exclusive intellectual property company, UMIP Ltd, updated software developed at the University of Manchester for incorporation into their VnmrJ software, giving Varian/Agilent a key competitive advantage. *“Since incorporation of the advanced tools supplied by your group for DOSY data collection and analysis into our software suite in 2009 we have licensed 51 copies of your program to academic and 31 copies to*

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industrial customers in connection with new instrument sales ... The 82 instruments referred to here cost between US\$250k and several \$m each and, therefore, DOSY has given this manufacturer of NMR equipment a competitive advantage that has contributed to several \$10m's of instrument sales since 2009. *It is rare, almost exceptional, that beyond producing breaking scientific results and first class publications, a research group puts so much extra effort into making their developments widely accessible and usable by the whole NMR community.*" (Applications Scientist, Agilent) [B].

5. Sources to corroborate the impact

The following users of DOSY have provided corroborative factual statements.

- A. Vice-President R&D, MestreLab (Spain, industry). Corroboration of impact in the pharmaceutical industry.
- B. Applications Scientist, Agilent (Germany, industry). Corroboration of incorporation in commercial instrumentation.
- C. Researcher, Givaudan (Netherlands, industry). Corroboration of role in identifying new flavour ingredients and resultant sales revenue.
- D. Researcher, Syngenta (UK, industry). Corroboration of role in plant protection formulations.
- E. Researcher, DuPont (US, industry). Corroboration of utilisation in industrial projects.